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EDITORIAL COMMENT

Shared Risk Factors for Anticoagulation in Nonvalvular Atrial Fibrillation

A Dilemma in Clinical Decision Making*

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Atrial fibrillation (AF) is the most common cardiac rhythm disorder (1) and can result in negative cardiovascular outcomes such as stroke and mortality, especially in patients with cardiovascular morbidities (2,3). AF also contributes substantially to the cost of medical care (4), of which stroke-related care is a large component. Clinical trials have fundamentally supported the concepts used by clinicians in the management of AF including rate and rhythm control, use of interventional procedures such as ablation, and anticoagulation for the prevention of stroke and thromboembolism (5,6). Despite these guidelines, there is no clear consensus in real-world practice on how AF patients should be managed with respect to the available data, with the exception that patients with AF and risk factors for stroke should be treated with an anticoagulant in the absence of a contraindication to such an agent. Despite the relative lack of controversy surrounding AF and anticoagulation in appropriate patients, anticoagulants are underutilized by cardiovascular specialists and even more so by primary care providers. The recent American College of Cardiology PINNACLE (Practice Innovation and Clinical Excellence) registry data showed a rate of only 57% for anticoagulant use in AF patients (7). The reasons for such underutilization are many and have not improved significantly even with the availability of warfarin alternatives over the past few years. These "novel oral anticoagulants" or "target-specific oral anticoagulants" have shown efficacy that is either improved or comparable to that of warfarin (8,9) but have not markedly increased the rate of overall anticoagulation use in appropriate AF patients.

See page 2141

Much of the focus on anticoagulation in AF has been in data demonstrating the efficacy in reducing stroke and thromboembolism. However, it is the other side of the coin, specifically, the concern over bleeding that has limited the adoption of anticoagulants in AF patients. In this issue of the *Journal*, Hylek et al. (10) present data from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial regarding the on-treatment safety population ($n = 18,140$ patients). In comparison to well-managed warfarin anticoagulation, apixaban therapy was associated with demonstrated benefits in adverse bleeding outcomes including a reduction in both intracranial and extracranial major hemorrhage (hazard ratio 0.69; $p < 0.001$). More importantly, these reduced adverse bleeding outcomes translated to a 50% decrease in total mortality in the next 30 days ($p < 0.001$). In addition, major extracranial hemorrhages on apixaban therapy resulted in fewer hospital stays, medical or surgical interventions, blood transfusions, and changes in anticoagulant therapy than on warfarin. The reduction in incidence of intracranial hemorrhage has been shown for the 3 currently approved novel anticoagulants (apixaban, dabigatran, rivaroxaban).

These findings highlight the need for a differential approach to anticoagulant therapy in AF. Hylek et al. (10) identified multiple independent risk factors such as older age, prior hemorrhage, prior stroke or transient ischemic attack (TIA), diabetes, lower hematocrit level, and renal dysfunction that were predictive of a first major hemorrhage. Female sex was also found in the multivariable model to have a lower risk of major hemorrhage. Not surprisingly, the use of aspirin and non-steroidal anti-inflammatory drugs increased the risk of major bleeding. Other than helping to elucidate predictors of major hemorrhage and to characterize major bleeding events, the most important aspect of this paper was the presentation of the concept of the "challenge of shared risk factors for stroke and hemorrhage among individuals with AF." Older age, previous stroke, and renal dysfunction were the most prominent factors for both stroke and major bleeding. These data clearly show that a singular approach toward anticoagulation for AF is not appropriate and that balancing the risk of ischemic stroke and thromboembolism with the risk of major bleeding is the preferred dual treatment target. This is most important in those patients with not only a high risk of ischemic stroke but also major bleeding. The identification of the at-risk population is the first step in addressing the net clinical benefit of targeted stroke reduction and reduced bleeding outcomes.

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Anticoagulation for AF is at a crossroads in therapy, with a movement toward novel anticoagulants as they provide either superior or noninferior ischemic stroke prevention and overall a comparable or reduced bleeding profile in comparison with that of warfarin. These new data for more specific, reduced bleeding outcomes with 1 of the novel anticoagulants, apixaban, adds more data to the movement away from warfarin for nonvalvular AF. In this investigation, warfarin use was associated with more major hemorrhage and more hospital stays for bleeding, transfusions, procedural interventions for bleeding, and changes in anticoagulant therapy which may have been related to the worse outcomes. Furthermore, as the authors note, the presence of agents that reverse the effect of warfarin by lowering the international normalized ratio does not necessarily have clear positive clinical outcomes. The novel anticoagulants offer advantages that argue for a lower threshold for anticoagulation (11). The message appears to be negative in the recent past regarding warfarin for AF, especially in light of the data for novel anticoagulants.

From a management standpoint, AF is best viewed as a "disease" with a variety of presentations from lone AF to one of many comorbid conditions, often in the very elderly. This heterogeneity makes the anticoagulation dilemma particularly difficult in terms of a recommendation to administer anticoagulants or not and which specific anticoagulant to use. Warfarin therapy reduces stroke by 64% and is associated with a decrease in all-cause mortality in AF (3). There has been a recent decline in stroke mortality driven by a reduced incidence of stroke and lower rates of death when stroke occurs (12), perhaps in part due to warfarin and improved stroke management. An analysis of warfarin use in Medicare beneficiaries from 2000 to 2010 was associated with reductions in stroke, hospital stays, and mortality across the Medicare population (13). Furthermore, from a value-based analysis of quality adjusted life years, warfarin may have economic value in the cost-constrained health system which exists today (14).

Despite the increasingly more positive data regarding novel anticoagulants, warfarin should not be abandoned nor overly ostracized for its negative points. Rather, it should be viewed as 1 of multiple choices in the tool box of anticoagulants that may be used for the shared risk assessment in determining the choice of anticoagulant therapy or no therapy in low risk or contraindicated patients. Underscoring this clinical dilemma of anticoagulant choice is the poor performance of clinicians in prescribing anticoagulants for AF in general. This fact may be the more important public health and quality of care issue. Other than more comprehensive risk assessment for net clinical benefit with equal consideration of both ischemic stroke and bleeding potential, efforts should be directed to improve anticoagulation rates in appropriate AF patients. The implementation of publically reportable performance measures and cardiovascular outcomes, readily available clinician and health system feedback, and financial risk would likely improve anticoagulation rates beyond medical education. The potential availability of functional antidotes for the novel anticoagulants or major cost reductions such as generic options in the future will also drive anticoagulation use upward.

A dilemma can be viewed as a problem offering 2 possibilities, neither of which is practically acceptable, or rhetorically, that you must accept 1 of the choices with each leading to some undesired conclusion. Yes, anticoagulation in AF is a clinical dilemma, but substantial amounts of data support the therapy. Clinicians do not see the strokes prevented, but they do see occurrences of major bleeding. Data from this investigation provide more support for a more complete view beyond efficacy of ischemic stroke reduction by including more concrete data for major bleeding, with a comparative perspective to well-managed warfarin therapy. Much more data are needed in this area to fill gaps in knowledge through continued research, especially in subgroups of patients in different clinical scenarios and with multiple comorbidities. Evaluation of racial and sex disparities would also be beneficial. Where data are lacking, it is hoped that the various specialty medical societies can provide recommendations to clinicians, using the best available evidence to date. Most of what happens in health care is provider-dependent and through the use of cardiovascular outcomes as the guide to navigate through the dilemma, both individual- and population-level benefits for our AF patients can be achieved.

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REFERENCES

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006; 114:119–25.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.
4. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011; 4:313–20.
5. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM III, et al., for 2006 ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation Writing Committee. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:223–42.

6. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14:528–606.
7. PINNACLE Registry Update. Cardiovascular Care Facts: A Report from the National Cardiovascular Data Registry. September 18, 2013.
8. You JJ, Singer DE, Howard PA, et al., for the American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e531S–75S.
9. Furie KL, Goldstein LB, Albers GW, et al., for American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council of Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:3442–53.
10. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): predictors, characteristics, and clinical outcomes. J Am Coll Cardiol 2014;63:2141–7.
11. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2011;4:14–21.
12. Lackland DT, Roccella EJ, Deutsch AF, et al., for American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, and Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke 2014;45:315–53.
13. Kim MH, Puckrein GP, Cai Q, Xu L. The relationship between patient diversity and warfarin use in atrial fibrillation: a ten year perspective (2000–2010) on cardiovascular outcomes. Circ Cardiovasc Qual Outcomes 2013;6:A9.
14. Canestaro WJ, Patrick AR, Avorn J, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circ Cardiovasc Qual Outcomes 2013;6:724–31.

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